REMARKS

Claims 1-2, 4-13, 15-18, 48, 49, 51, 52, 56-60, 65, 66, 70-73, 77, 79, 83-88, 90, 91, 93, 99-102 are pending in this application, of which Claims 4-13, 15-18, 48, 49, 52, 58-60, 66, 70-72, 84-87, 90, 91, and 93 are presently withdrawn.

Applicants respectfully reserve the right to pursue any non-elected, cancelled or otherwise unclaimed subject matter in one or more continuation, continuation-in-part, or divisional applications.

Reconsideration and withdrawal of the objections to and the rejections of this application in view of the amendments and remarks herewith, are respectfully requested, as Applicants submit that the application is in condition for allowance.

Rejections under 35 U.S.C. § 103(a)

Claims 1, 2, 37, 51, 56, 57, 65, 73, 77, 79, 83, 88, and 89 are rejected under 35 U.S.C. 103(a) as unpatentable in view of Huang *et al* (*Analytical Biochemistry*, 1999, IDS) ("Huang") in view of Imaizumi *et al* (*Journal of Physical Chemistry,* 1995) and Xu *et al* (*Tetrahedron Letters,* 2001).

The Office Action alleges that Huang teaches a method of preparing a sample for mass spectrometry analysis comprising "reacting the analyte with a triaryl phosphionium labeling reagent (Tris(trimethoxyphenyl)phosphonium(TMPP) reagents) having a reactive group." Indeed, Huang only teaches the use of Tris(2,4,6-trimethoxyphenyl)phosphonium reagents.

Claims 1, 88, 99 and 100 are rejected under 35 U.S.C. 103(a) as unpatentable in view of Leavens *et al* (Rapid Communications in Mass Spectrometry, 2002, IDS) ("Leavens") in view of Imaizumi *et al* (*Journal of Physical Chemistry,* 1995) and Xu *et al* (*Tetrahedron Letters,* 2001).

The Office Action alleges that Leavens teaches a method of preparing a sample for mass spectrometry analysis comprising "reacting the analyte with a triarylphosphionium labeling reagent

(TMPP-reagents) having a reactive group." Indeed, Leavens only teaches the use of TMPP reagents.

With regards to Claims 88, 99, and 100, the Examiner states that "while Huang does not specifically teach that the sample is a biological tissue, it is well known that proteins can be obtained from biological tissue." Similarly, the Examiner states that "Leavens teaches analyzing amines and carboxylic acid compounds" but while Leavens "does not teach that the sample , the Examiner states that while "Leavens does not specifically teach that sample is a biological tissue. It is well known that amines can be obtained from biological tissue."

Again, Applicants respectfully assert that **Claims 88, 99, and 100 do not relate to the use of a protein or an amine *from* a biological tissue as a sample, but instead Claims 88, 99, and 100 relate to the use of a *biological tissue as the sample itself.*** Although Applicants agree that proteins and amines can often be obtained from a biological tissue, Applicants respectfully disagree that obtaining a protein or an amine from a biological tissue as a sample for mass spectrometry analysis and using the biological tissue itself as a sample for mass spectrometry analysis would be seen as obvious variations.

Indeed, a biological tissue may comprise other types of molecules (small molecules, non-proteinaceous compounds) which can be analyzed by Mass Spectrometry and which may be of importance to one skilled in the art. As such, Applicants respectfully contend that one of ordinary skill in the art, upon reading of the use of proteins as a sample in Huang or amines as a sample in Leavens would have had **no motivation and no reasonable expectation of success in using a *biological tissue itself* as a sample** for Mass Spectrometry.

Furthermore, Applicants note that Claims 101-102 are not specifically rejected in the body of the Office Action, though they are listed as rejected on the Office Action Summary. Applicants respectfully reassert that Claims 101 and 102 - directed to methods in which the biological sample are not further cleaned-up or desalted after labeling – are novel and nonobvious in

light of the art cited. Nothing in Huang or Leavens teaches or suggests the analysis of an analyte biological tissue sample without further clean-up or desalting.

Applicants respectfully assert that neither Huang nor Leavens renders the claimed invention obvious.

The Examiner has relied on Imaizumi and Xu to argue that one of ordinary skill in the art would have readily substituted the trimethoxyphenyl group of the prior art references with the Ar_3P group of the claimed invention because the Ar_3P groups would have been expected to delocalize the positive charge of the phosphine through the conjugated pi orbitals of the flurophores.

The Examiner further contends that the steric bulk of the trimethoxyphenyl group of the prior art and the Ar_3P group of the claimed invention would be the same as a result of the molecular weight. Applicants respectfully note that steric bulk and molecular weight are different factors. Indeed, just because a molecule has a heavier element (such as oxygen) present in its formula, the steric geometry of the molecule may still be relatively small.

Nevertheless, Applicants contend that one of ordinary skill in the art would still have had no reasonable expectation of succcess in achieving the surprising results of the claimed invention. Indeed, the claimed invention, in addition to increasing the sensitivity of analysis of an analyte by mass spectrometry, also provides increased sequence coverage and increased ionization efficency, thereby allowing for desorption/ionization of molecules in a biological tissue at the picomole, femtomole, and attomole amounts. Furthermore, the methods of the claimed invention provide increased ionization of hydrophobic peptides, and simplified sample preparation as desalting is not necessary. See. for example, Page 3, lines 31-33 and Page 4, lines 12-17.

Nothing in Huang not Leavens describes this increased efficiency, particular with regard to the testing of a biological tissue. Indeed, at best, one of ordinary skill in the art would reas Huang and Leavens as providing only increased sensitivity of pre-digested or otherwise fragmented peptides. One of ordinary skill in the art would have no reasonable expectation of success in

achieving the increased effeciency of ionization of the analytes of interest from a biological tissue as provided by the claimed invention.

As such, applicants contend that one of ordinary skill in the art would have had no motivation to modify the TMPP reagents of Huang or Leavens to arrive at the labeling reagents of the instant claims.

Applicants respectfully request that the rejections of the claims under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

In view of the remarks made herein, Applicants submit that the application is in condition for allowance. Accordingly, Applicants respectfully request entry of the amendments and remarks presented herein, favorable reconsideration of the application and prompt issuance of a Notice of Allowance. If a telephone conference with Applicants' representative would be helpful in expediting prosecution of the application, Applicants invite the Examiner to contact the undersigned at the telephone number indicated below.

Applicants believe that no additional fees, other than the extension of time fees, are required in connection with this paper. Nevertheless, Applicants authorize the Director to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to Deposit Account No. 04-1105, under Order No. 64254(49991).

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Respectfully submitted,

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